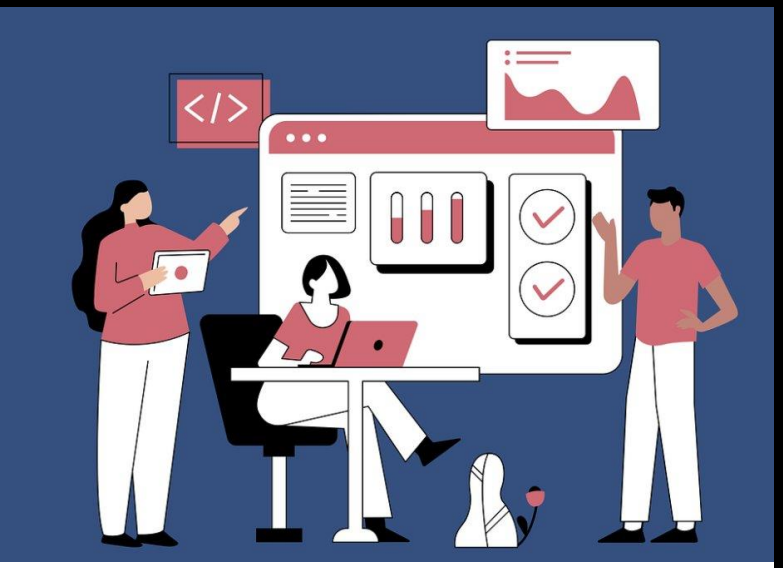

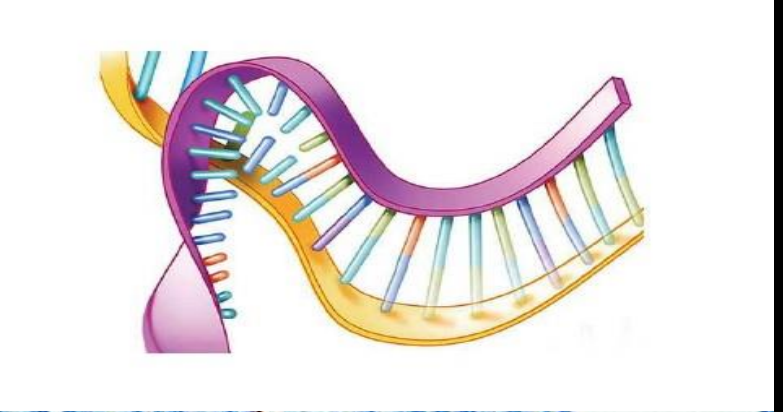

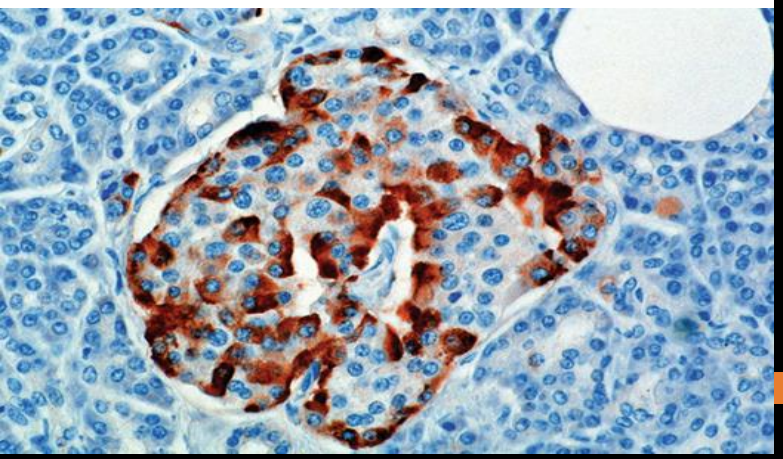

Interhospital Endocrine Conference 2022

HNF1B-MODY (MODY5)

YOTSAPON THEWJITCHAROEN, M.D.

Endocrinologist, Diabetes and Thyroid center,

Theptarin Hospital

June 2022

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Actionable MODY: GCK and HNF series

- GCK-MODY: unnecessarily treated with a variety of medications
- HNF1A/HNF3A/ABCC8/KCNJ11 (which respond to sulfonylurea treatment)
- HNF1B (diabetes with renal cysts and/or other genitourinary defects and other associated features)
- m.3243A>G (the most common mitochondrial mutation causing maternally inherited diabetes and deafness)

CHALLENGES IN MONOGENIC DIABETES

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CHALLENGES AND OPPORTUNITIES IN DIAGNOSIS AND TREATMENT

- The presence of a monogenic form of diabetes should be considered when a patient does not seem to fit with the more common presentations of type 1 or type 2 diabetes
- Decades of research on different populations have shown that any stringently defined set of features will be too restrictive to identify all people who carry a highly penetrant genetic variant.
- No approach will be sensitive enough to accurately detect every case or specific enough to ensure that genetic testing is not performed on patients who turn out not to have a monogenic diagnosis.

Accessing Genetic Testing

- Decisions on testing rest with individual clinicians.
- This dilemma occurs especially with patients in youth or young adulthood, when the more common forms of monogenic diabetes are most likely to become apparent.
- Some patients who are unlikely to have MODY are tested, whereas many who are very likely to have MODY are not.

Accessing Genetic Testing

- **In most industrialized countries, molecular genetic testing for MODY is available, but in many regions throughout Asia and Africa, samples must be sent to distant laboratories outside of the patient's country of residence.**
- **The cost of genetic testing, like that of other technology- related services, is likely to decline, *but a significant decrease has not yet occurred.***

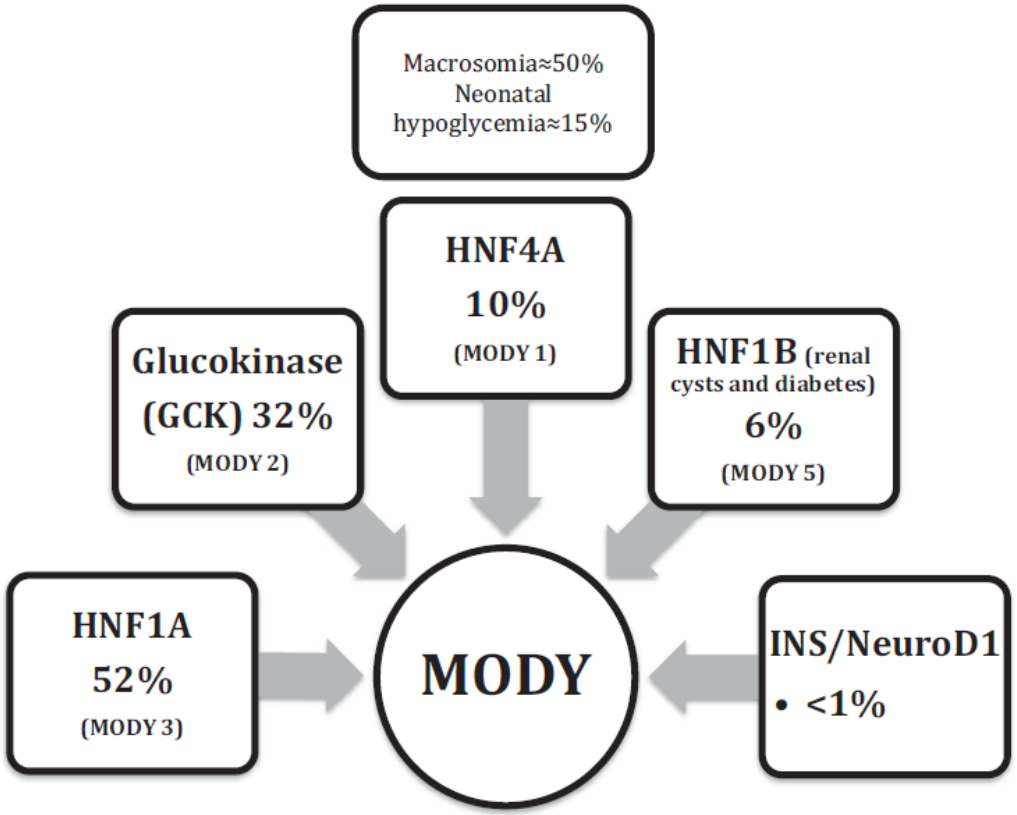
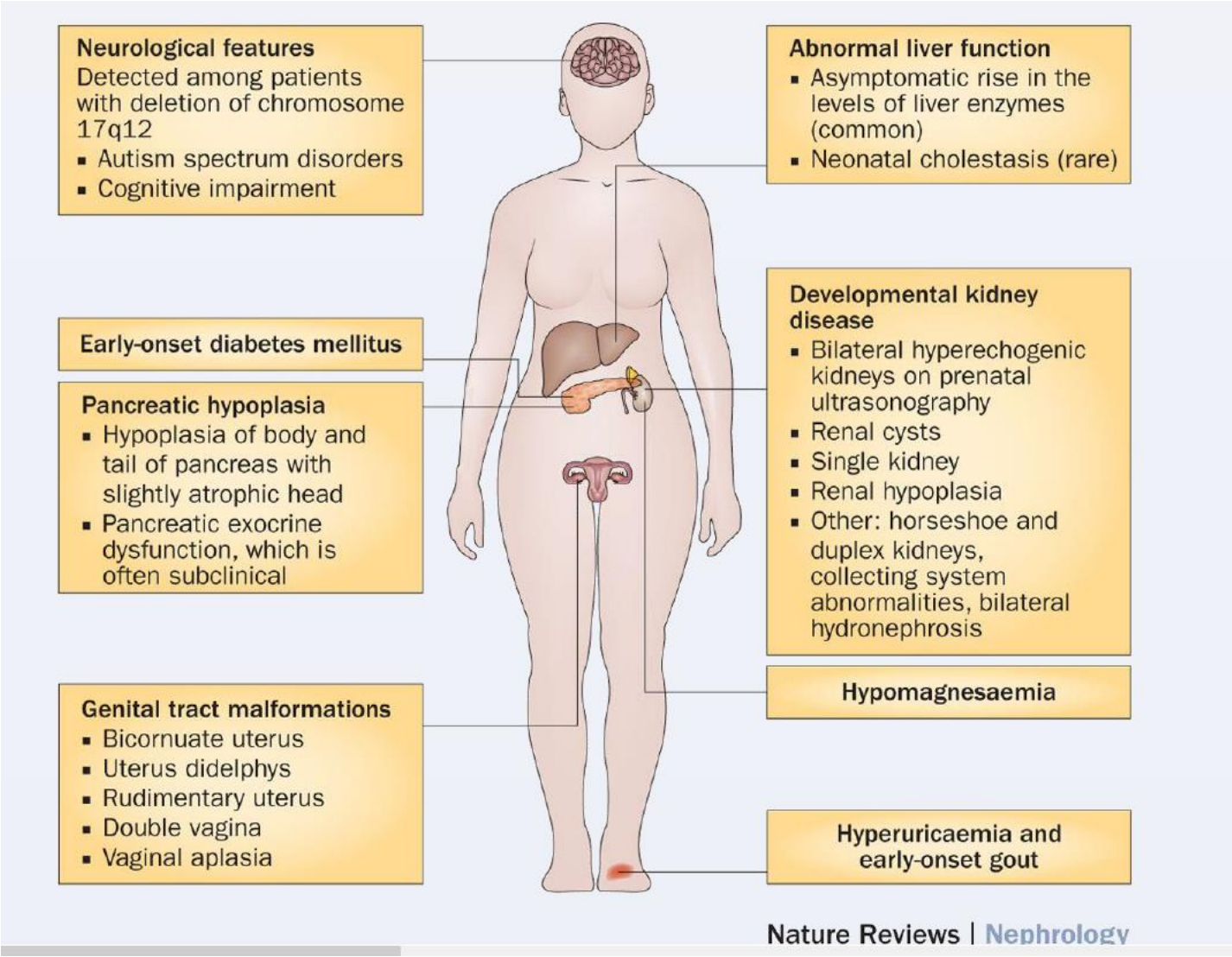


Figure 1. Distribution of monogenic diabetes (10,15).



Nat Rev Nephrol 2015;11:102-12.

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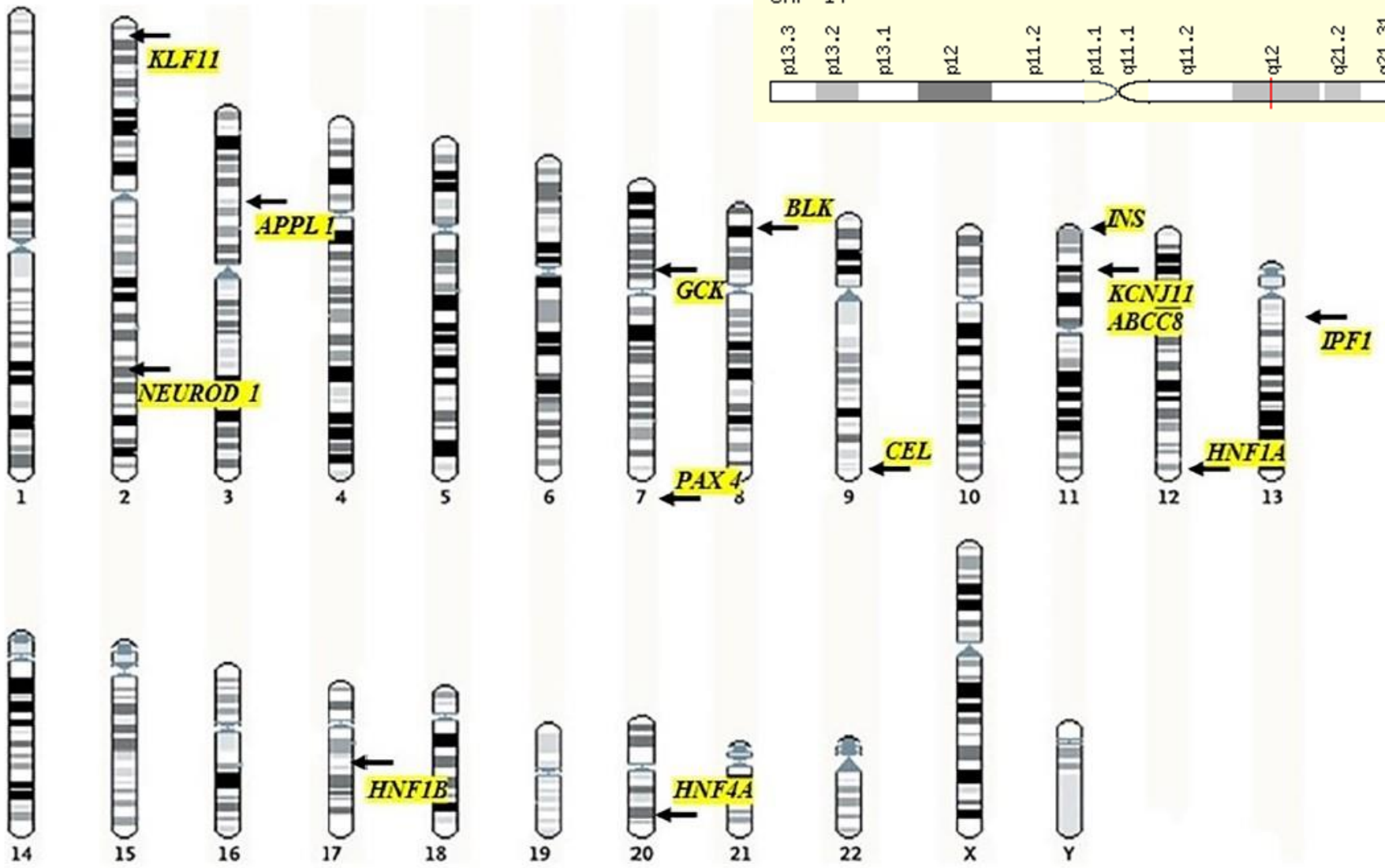

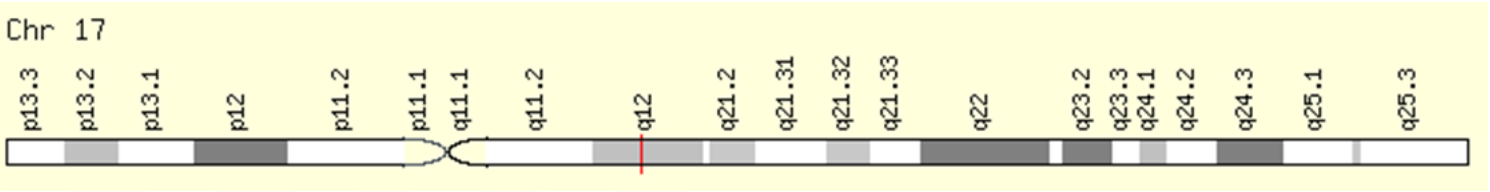

Fig. 1. A karyogram of the common and rarer types of MODY.

J Diabetes Complications 2021;35: 107640.

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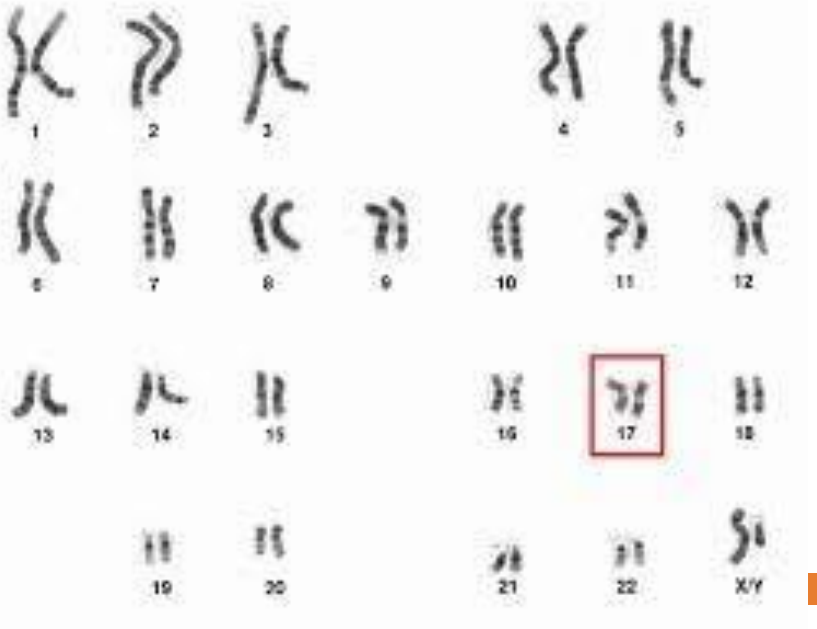
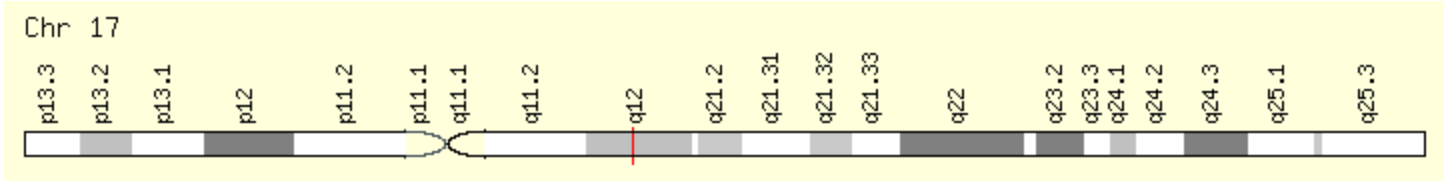
HNF1B-MODY (RCAD)

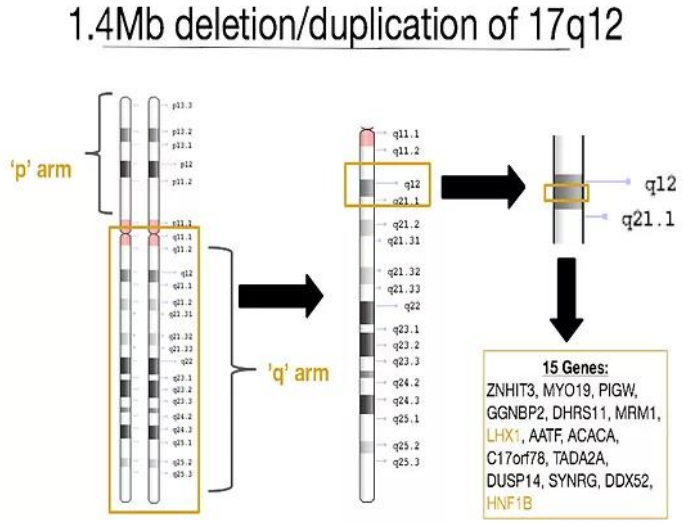
- HNF1B-MODY is typically characterized by renal cysts and diabetes but can feature developmental anomalies in multiple systems.
- This form of diabetes typically starts in adolescence or early adulthood, is usually insulin-requiring, and may be insulin-dependent because the etiology is a reduced number of b-cells in development.
- Reduced pancreatic tail size or low fecal elastase can aid diagnosis of exocrine pancreatic insufficiency.

MODY5-related to 17q12 microdeletion syndrome

- The gene encoding hepatocyte nuclear factor 1β *(HNF1B)*, a transcription factor involved in the development of the kidney and other organs, is located on chromosome 17q12. The 17q12 is a typical hot spot for chromosomal deletion and could have complicated the clinical heterogeneity of MODY5.
- The 17q12 microdeletion syndrome should be suspected in individuals with a deletion of *HNF1B* identified on gene-targeted deletion/duplication analysis







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Genomic Testing Used in 17q12 Deletion Syndrome

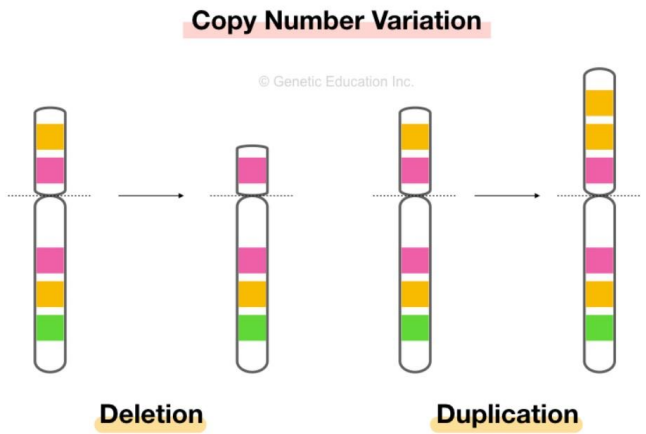
- The17q12 recurrent deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic techniques.

- Genomic testing methods that determine the copy number of sequences can include chromosomal microarray (CMA), exome sequencing with CNV calling, genome sequencing, or targeted deletion analysis.

- Copy number variant-calling algorithms need to be utilized to detect the 17q12 recurrent deletion.

Low-pass Genome Sequencing (GS) V.S. Chromosomal Microarray Analysis (CMA)

- DNA **copy-number variants (CNVs)** detection by CMA is based on probe density, which varies among different CMA platforms, versions, and designs within the targeted regions.
- Applying CNV analysis based on low-pass (or low-coverage) GS provides better sensitivity and specificity of CNV detection due to the increased uniformly distributed/aligned reads.



Chromosomal deletion and duplication and copy number variation.

Curr Protoc Hum Genet. 2017;94:11-8.

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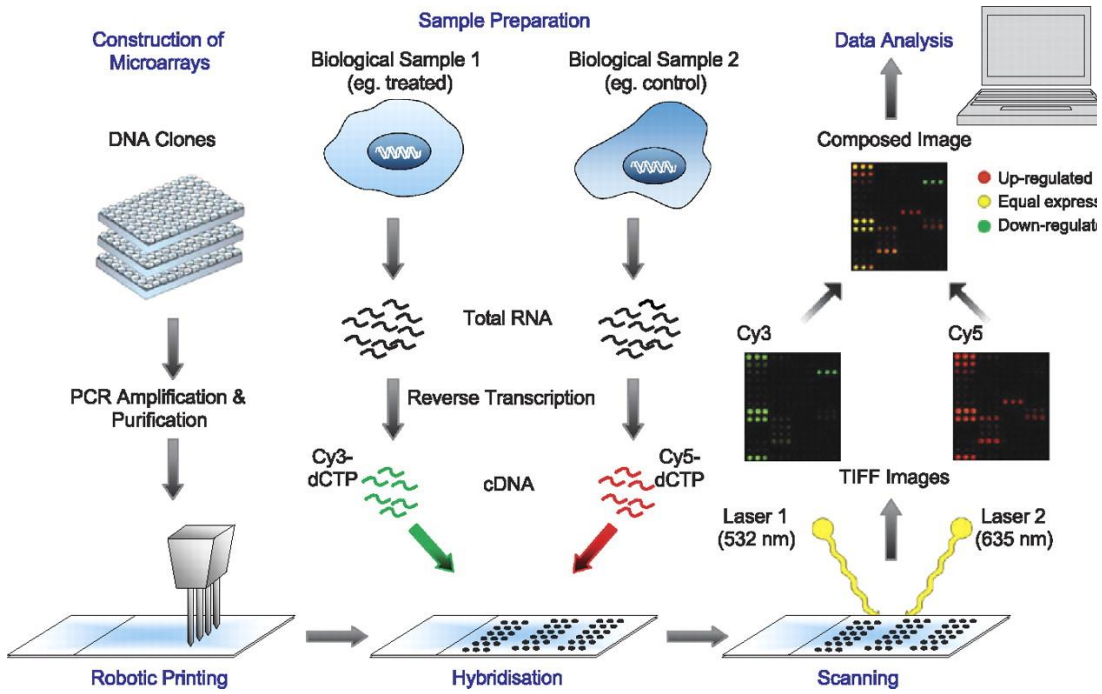
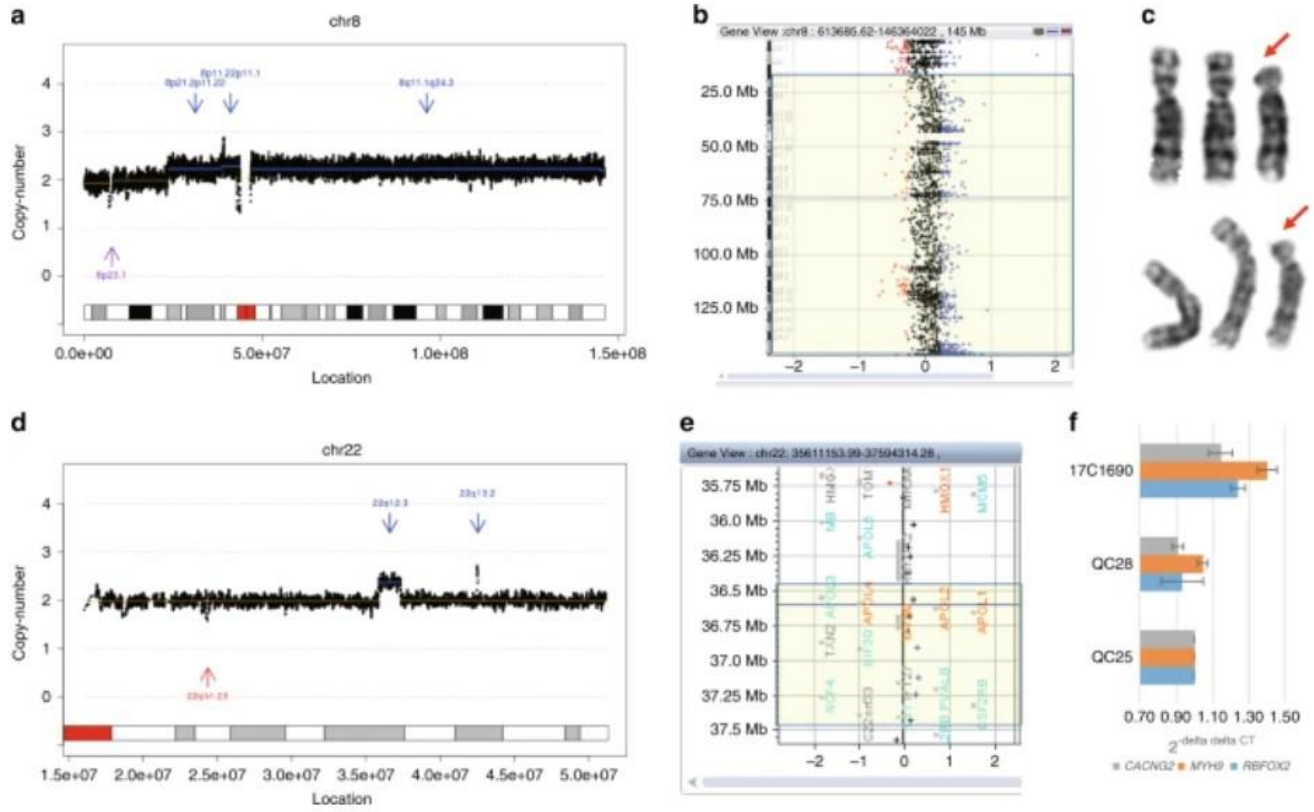


Fig. 3



Low-level mosaicism defined by low-pass genome sequencing (GS). (**a**) Low-pass GS identified a partial trisomy 8 (indicated by three blue arrows) at an approximately 23% mosaic level in 19C1149 involving the centromere. (**b**) Probe distribution in chromosomal microarray (CMA) with the candidate

Low-Pass Genome Sequencing to detect CNVs

Genetics in Medicine 2020; 22: 500–10.

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Table 2. Tissue-specific expression of HNF family members in human embryonic and adult tissues.

		Brain	Endocrine tissues*	Bone marrow & immune system	Muscle tissues	Lung	Liver and gall bladder	Pancreas	Gastrointestinal tract	Kidney & urinary bladder	Male reproductive tissues	Female reproductive tissues	Adipose & soft tissue	Skin
Human embryo	HNF1α						■	■	■	■				
	HNF1β							■	■	■				
	FOXA1					■	■		■					
	FOXA2					■	■	■	■					
	FOXA3						■		■					
	HNF4α						■	■		■				
	HNF4γ						■		■	■				
Adult human	HNF1α			■			■	■	■	■				
	HNF1β			■		■	■	■	■	■	■	■		
	FOXA1			■		■	■		■	■	■	■		
	FOXA2			■		■	■	■	■		■	■		
	FOXA3	■	■	■	■	■	■	■	■	■	■	■	■	■
	HNF4α		■	■	■		■	■	■	■	■		■	■
	HNF4γ	■	■	■	■	■	■	■	■	■	■	■	■	■
	OC1	■				■	■		■	■		■		
	OC2						■		■					

Information on embryonic tissue expression is extracted from "An integrative transcriptomic atlas of organogenesis in human embryos"[52] and consolidated from.[48,51] No information is available for ONECUT family members. Information on adult tissue expression is consolidated from[5,14,48,50] and adapted from the Protein Atlas database (http://www.proteinatlas.org/). Coloured squares denote expression. Endocrine tissues refer to thyroid, parathyroid and adrenal glands. FOXA, forkhead box A; HNF, hepatocyte nuclear factor; OC, ONECUT.

Journal of Hepatology 2018; 68:1033-48.

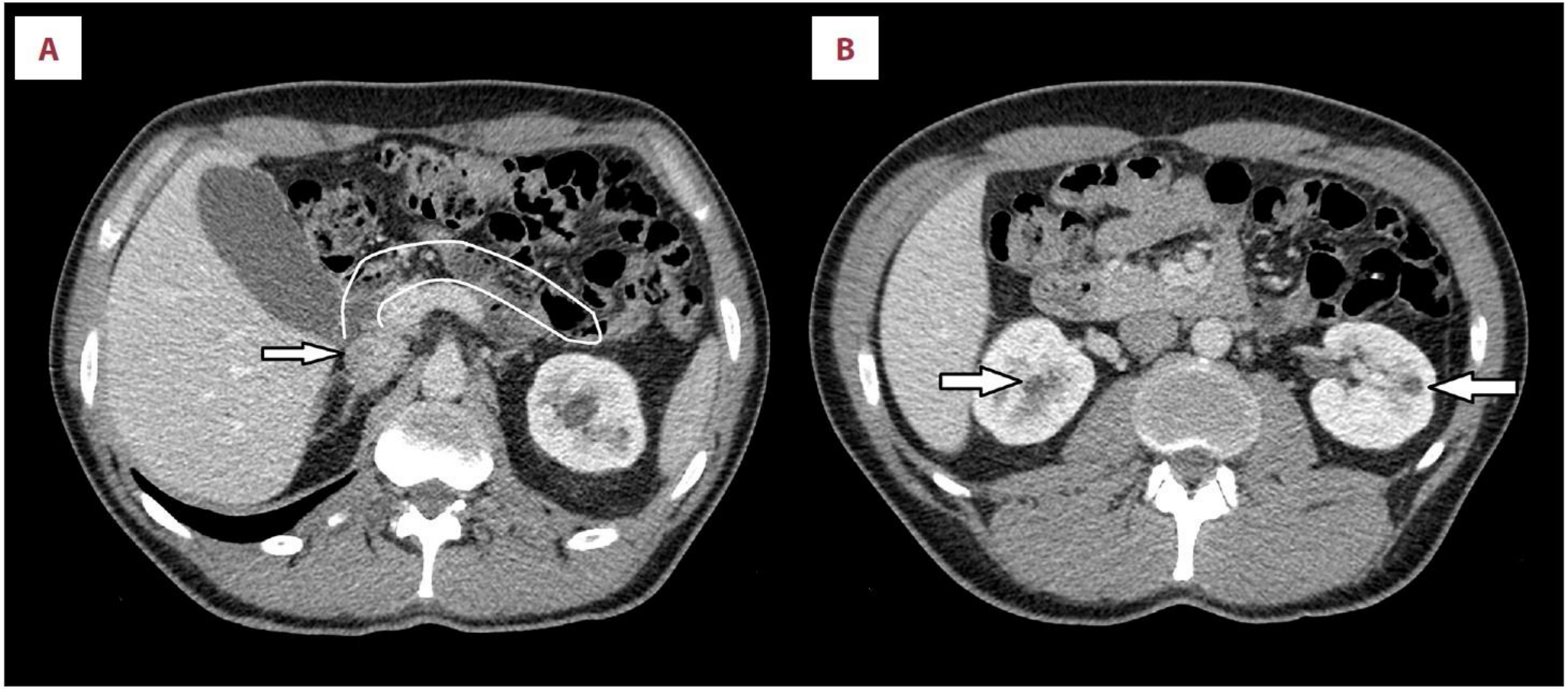

Figure 1. Axial contrast-enhanced computed tomography image showing the absence of the pancreatic body and tail. (**A**) The arrow shows the pancreatic head; (**B**) arrows identify the renal cysts.

Am J Case Rep 2021;22: e928994.

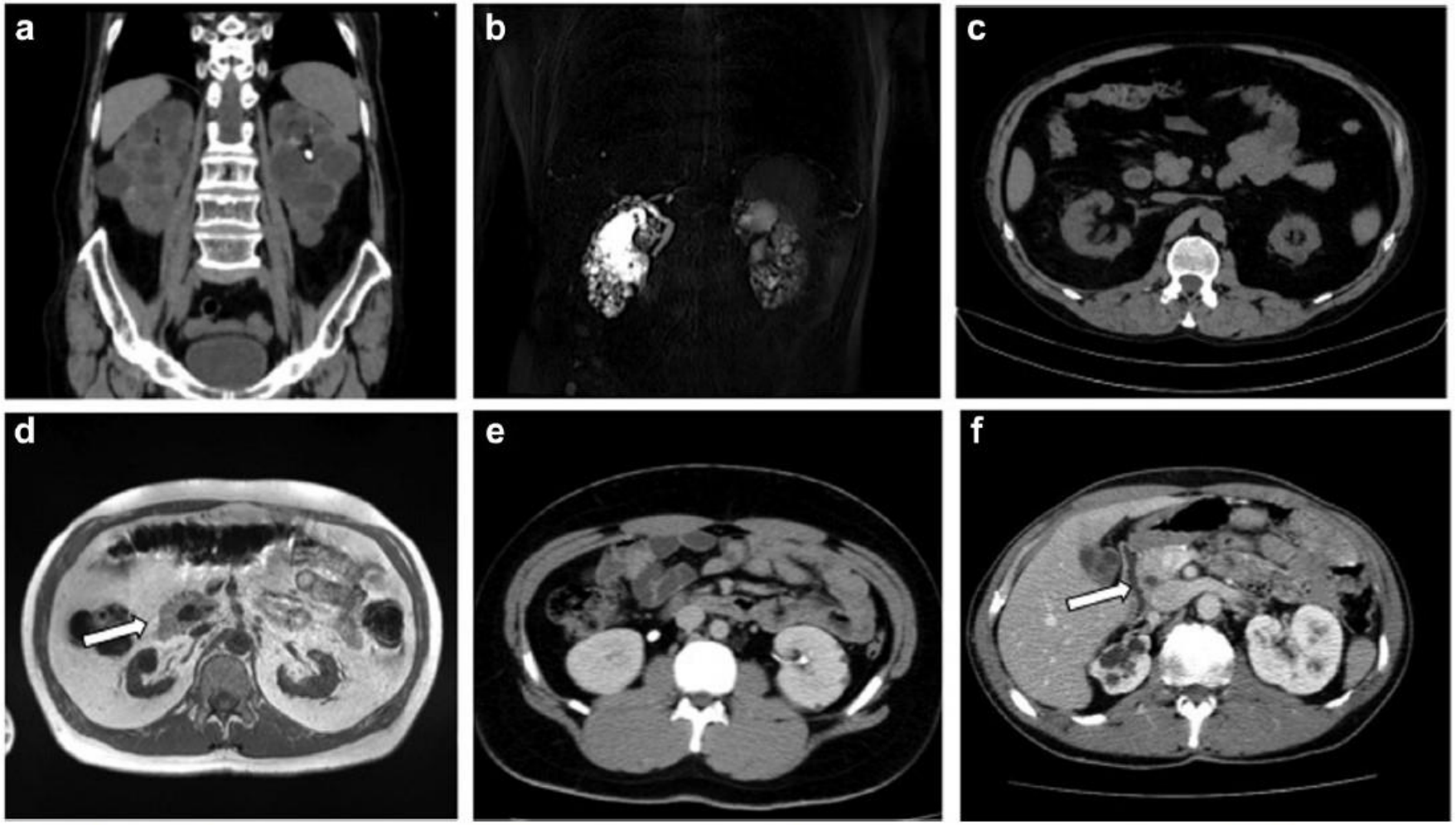

Figure 2. (a) I-1, family 1: computed tomography (CT) scan showing enlarged bilateral cysitc kidneys, left renal stone. (b) II-1, family 1: magnetic resonance imaging (MRI) scan showing multiple small bilateral kidney cysts in normal sized kidneys. (c) II-1, family 2: CT scan showing bilateral small kidneys and few cysts. (d) I-1, family 3: MRI scan showing bilateral small kidneys and annular pancreas (white arrow). (e) III-1, family 5: CT scan showing bilateral normal sized kidneys and several cysts. (f) I-1, family 6: CT scan showing right kidney hypoplasia with cysts, including multiple cysts in the left kidney and annular pancreas (white arrow).

Nomenclature

In 1997, heterozygous pathogenic variants in *HNF1B* were described as a cause of MODY in one family [Horikawa et al 1997]; shortly thereafter the same family was found to have kidney involvement [Iwasaki et al 1998]. In 2001, the combination of congenital anomalies of the kidney and urinary tract and MODY5 became known as "renal cysts and diabetes (RCAD) syndrome" [Bingham et al 2001].

Prevalence

The reported prevalence of the 17q12 recurrent deletion in large populations not selected on the basis of disease ranges from 0.002% (1:50,000) to 0.007% (1:14,000) – 0.002% in healthy European volunteers (UK Biobank; n = ~421K), 0.004% in a US health care system-based population (DiscovEHR; n = ~90K), and 0.007% in a large Icelandic control sample (deCODE; n = ~101K) [Martin et al 2020]. A higher prevalence estimate of 0.025% (1:4,000) was described in a population-based pregnancy cohort study of 12,252 mother-father-newborn trios [Smajlagić et al 2020].

Mitchel MW, Moreno-De-Luca D, Myers SM, et al. 17q12 Recurrent Deletion Syndrome. 2016 Dec 8 [Updated 2020 Oct 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.

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- Copy number variant-calling algorithms need to be utilized to detect the 17q12 recurrent deletion.

Estimated Prevalence of the 17q12 recurrent deletion

Among individuals undergoing clinical postnatal chromosomal microarray analysis, the prevalence of the 17q12 recurrent deletion is much higher: approximately 0.1% (1:1000) [Moreno-De-Luca et al 2010, Rosenfeld et al 2013, Kirov et al 2014, Rasmussen et al 2016]. The main indications for clinical CMA in these studies were neurodevelopmental disorders (global developmental delay, intellectual disability, ASD) and congenital malformations.

It may be useful to consider the estimated prevalence of the 17q12 recurrent deletion in certain clinical populations:

- Congenital anomalies of the kidney. 1.9% (~1:53); when considering CAKUT more broadly, 0.8% (~1:123) have 17q12 deletion [Verbitsky et al 2019].
- Chronic kidney disease. 0.03%-2.2% (~1:3000 - 1:46) [Lata et al 2018, Connaughton et al 2019, Groopman et al 2019]
- Neurodevelopmental disorders. 0.09% (~1:1,150) [Kirov et al 2014]
- Schizophrenia. 0.036% (~1:2,800) [Kirov et al 2014]
- Müllerian aplasia. 3%-6% (~1:33 - 1:17) [Nik-Zainal et al 2011, Williams et al 2017]. Among women with both uterine and kidney anomalies, 18% (~1:6) had a 17q12 deletion or pathogenic *HNF1B* sequence variant [Oram et al 2010].

Mitchel MW, Moreno-De-Luca D, Myers SM, et al. 17q12 Recurrent Deletion Syndrome. 2016 Dec 8 [Updated 2020 Oct 15]. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.

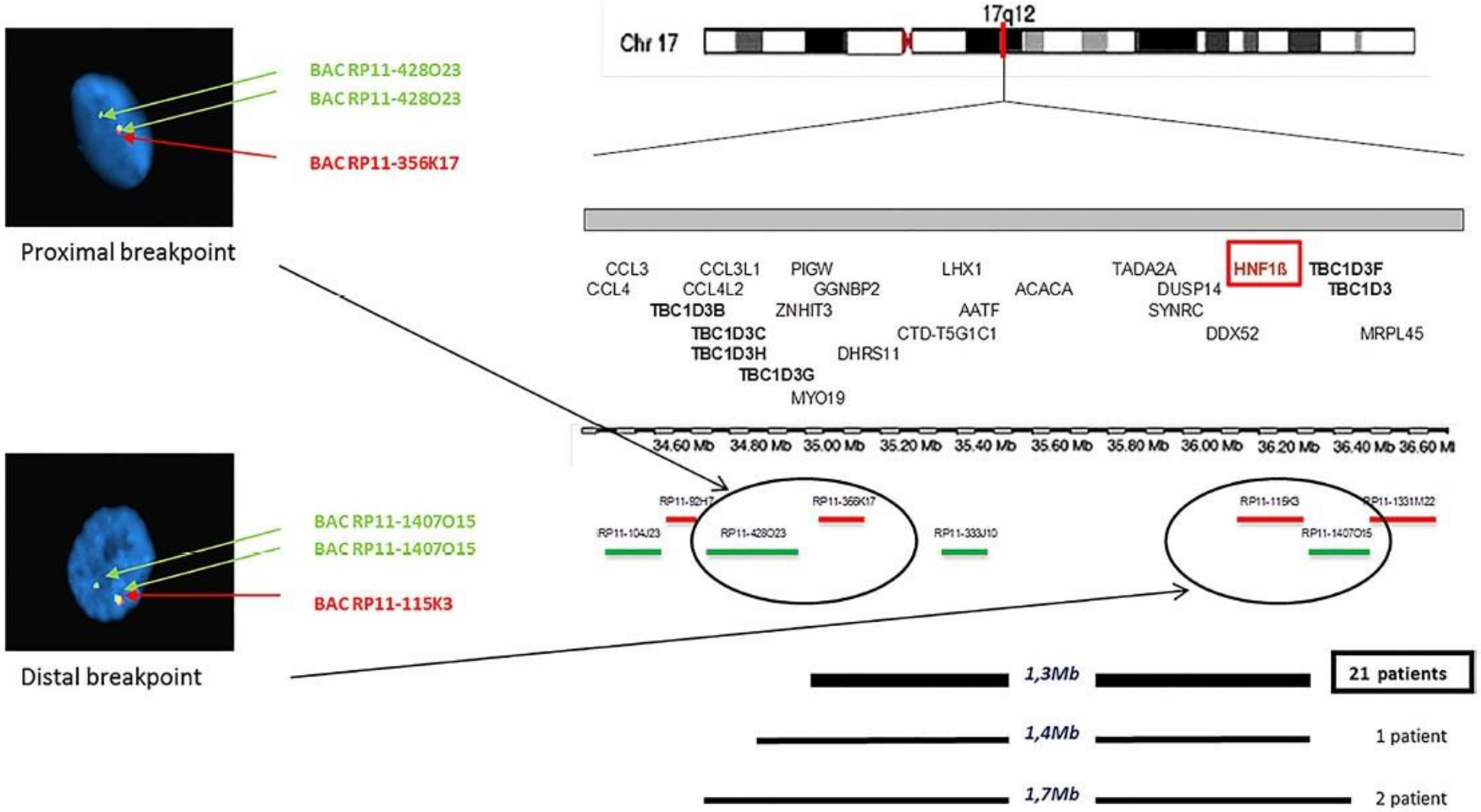

Figure 1 Details and results of fluorescence *in situ* hybridisation analyses on cells from buccal smears.

J Pathol 2021;254:31-45.

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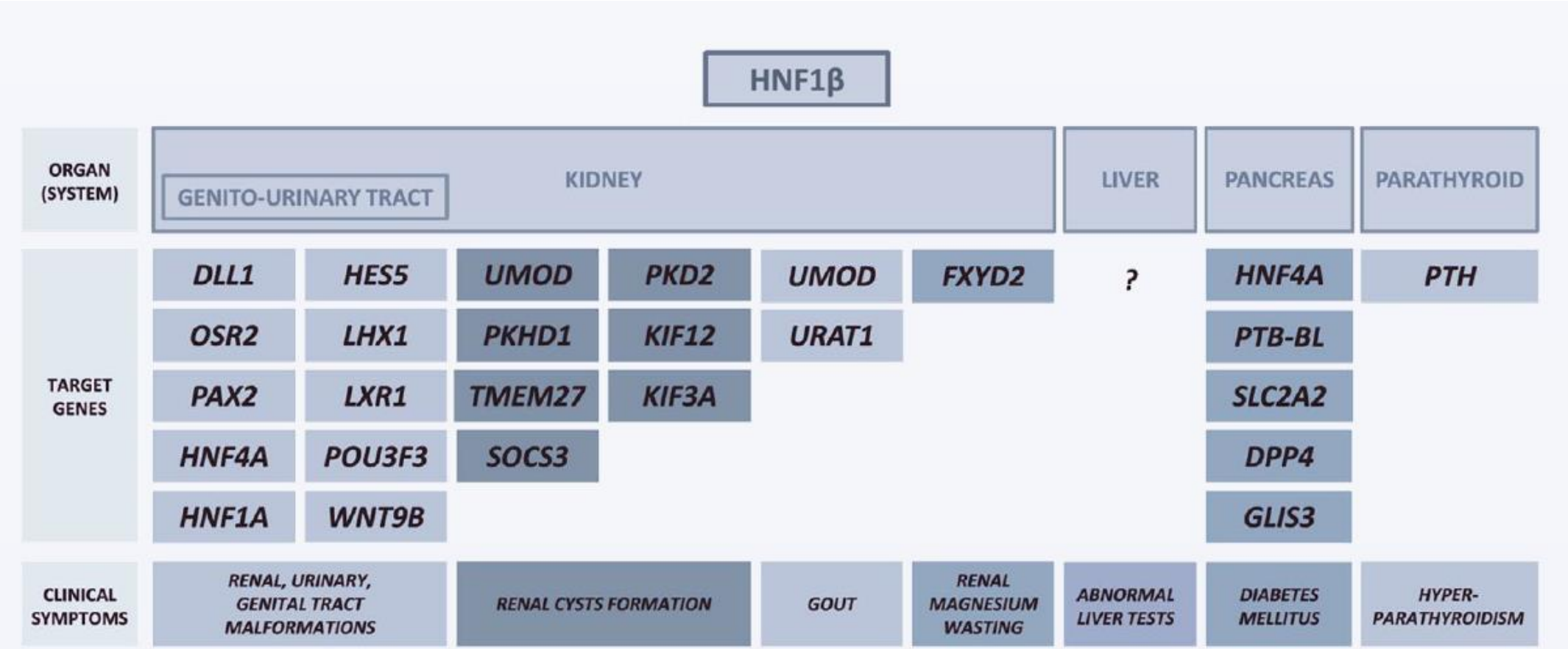

Figure 2. HNF1β as a promiscuous transcription factor. Target genes known to be regulated by the HNF1β transcription factor in several organ systems, responsible for the diverse multisystem clinical signs and symptoms, are depicted.

Diabetes 2021 Jun; 70(Supplement 1)
https://doi.org/10.2337/db21-16-OR

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Genes of interest in this region. Genes within the 17q12 recurrent deletion region include *AATF*, *ACACA*, *C17orf78*, *DDX52*, *DHRS11*, *DUSP14*, *GGNBP2*, *HNF1B*, *LHX1*, *MRM1*, *MYO19*, *PIGW*, *SYNRG*, *TADA2A*, and *ZNHIT3*.

Three genes are of particular interest with respect to phenotypes associated with the 17q12 recurrent deletion:

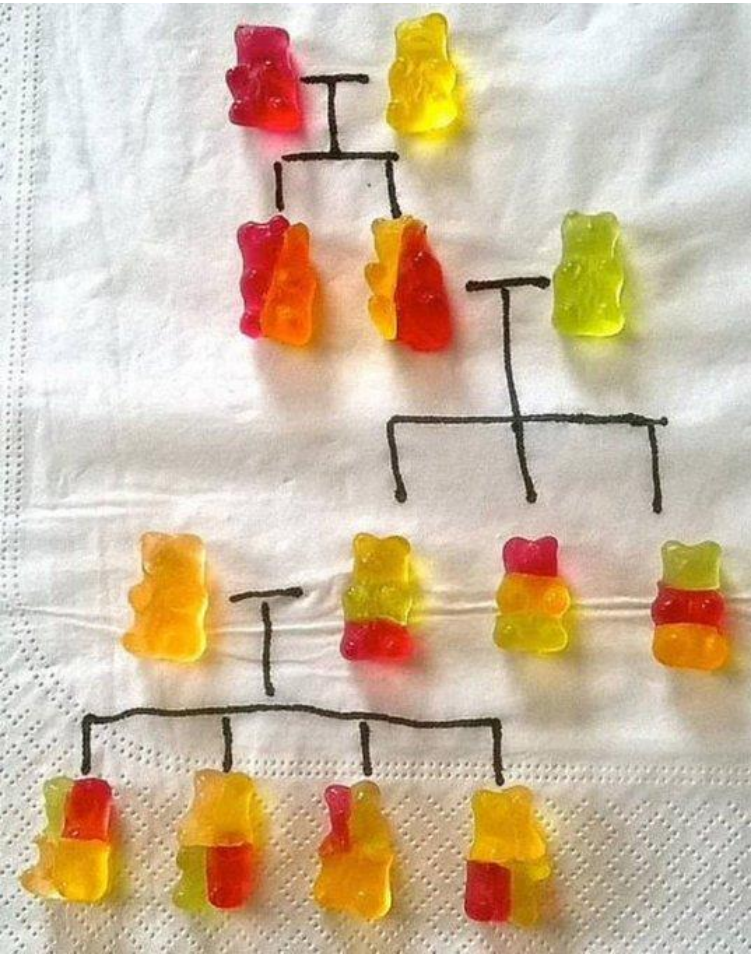
- ***HNF1B.****HNF1B* haploinsufficiency has been established as the cause of the kidney, urogenital, and endocrine abnormalities that occur as part of the 17q12 recurrent deletion syndrome. Heterozygous pathogenic sequence variants in *HNF1B* cause renal cysts and diabetes (RCAD) syndrome, which is characterized by the combination of congenital anomalies of the kidney and urinary tract (CAKUT) and maturity-onset diabetes of the young type 5 (MODY5) [Bingham et al 2001]. While other genes in the 17q12 recurrent deletion region likely account for most of the neurodevelopmental features associated with the syndrome, isolated sequence variants within *HNF1B* have also been associated with an increased risk for learning problems, albeit at a lesser frequency [Clissold et al 2016, Dubois-Laforgue et al 2017a, Lalière et al 2020]. Thus, more research is needed to define the role of *HNF1B* in the human brain.
- ***LHX1.*** Heterozygous *LHX1* likely pathogenic variants have been identified in females with müllerian aplasia / Mayer-Rokitansky-Küster-Hauser syndrome, though inheritance information was not available [Ledig et al 2011, Ledig et al 2012, Sandbacka et al 2013]. Because of its role in neural development, *LHX1* may also contribute to the neurodevelopmental manifestations observed in the 17q12 recurrent deletion syndrome [Moreno-De-Luca et al 2010, Nagamani et al 2010].
- ***ACACA*** encodes acetyl-CoA carboxylase 1, involved in lipogenesis in adipose tissue. There has been speculation that haploinsufficiency of *ACACA* may contribute to the leaner phenotype and decreased risk of diabetic glomerular disease in individuals with the 17q12 recurrent deletion compared to those with *HNF1B* sequence variants [Dubois-Laforgue et al 2017b].

Three facial dysmorphic features in 17q12 microdeletion
High forehead (75%), Deep set eyes (65%) and Chubby cheeks (75%)

Figure 4 Facial phenotypes of patients with 17q12 microdeletion.

Laffargue F, *et al*. *Arch Dis Child* 2015;**100**:259–264. doi:10.1136/archdischild-2014-306810

MODY: Search and you will find it!



Many patients with MODY, especially the glucokinase MODY, can be first diagnosed during pregnancy.

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Take ZOOM messages

- Making a correct molecular diagnosis is crucial, as this allows optimal treatment and therefore the best long-term outcome for MODY patients.
- Patients with a strong family history of diabetes at young ages and renal morphologic abnormalities diagnosed at or soon after birth should be considered for the *HNF1B* screen.
- HNF1B-associated MODY is a multisystem disease and includes genital tract malformation, abnormal liver function test, hypomagnesemia, and hyperuricemia associated early gout; neurological features.
- 17q12 microdeletion syndrome could have complicated the clinical heterogeneity of MODY5.

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